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[54] Title: CONTRAST AGENT FOR ULTRASONIC DIAGNOSIS

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1. Title

CONTRAST AGENT FOR ULTRASONIC DIAGNOSIS

2. Claims

1. Contrast agent for ultrasonic diagnosis characterized by the fact that its primary component is a perfluorocarbon emulsion with an emulsion particle size of 1-10 μm.

2. Contrast agent for ultrasonic diagnosis in accordance with Claim 1, characterized by the fact that the perfluorocarbon concentration is 25-100 w/v%.

3. Contrast agent for ultrasonic diagnosis in accordance with Claims 1 and 2, characterized by the fact that the perfluorocarbon is perfluoro-N-methyldecahydroisoquinoline.

4. Contrast agent for ultrasonic diagnosis in accordance with Claims 1, 2 and 3, characterized by the fact that it is used for ultrasonic diagnosis in the heart.

3. Detailed Description of the Invention

<Industrial Field of Application>

The present invention concerns a contrast agent for ultrasonic diagnosis whose primary component is a perfluorocarbon emulsion with an emulsion particle size ranging from 1 to 10 μm.

<Prior Art>

In ultrasonic imaging of the heart (contrast echo techniques), a contrast agent is injected into a peripheral vessel in order to obtain information about cardiovascular blood flow. It can be likened to cardioangiography, a form of radiography. This imaging method is extremely useful clinically, and a wide range of applications have been devised for analyzing hemodinetic information such as [the presence of] shunts and the direction, speed, and pattern of blood flow.

Contrast agents that have been used in the prior art include physiological saline solutions, 5% saccharide solutions, autologous blood, indocyanine green, and Urografin. All of these substances are mixed with air either by hand or with a sonicator, and the resulting air bubbles are used as echo sources. However, these agents do not provide satisfactory contrast echoes in all patients, may fail to provide good contrast echoes, or may not provide them with good reproducibility with repeated injections. Even if the method is extremely useful clinically,

it will provide very little diagnostic information if satisfactory contrast echoes are not obtained [sic]. Thus, a major obstacle to this examination method at present is the failure to provide satisfactory contrast echoes in all patients. Furthermore, the contrast echoes provided by the contrast agents now in use, such as those mentioned herein above, cannot transverse the pulmonary capillaries and usually do not appear in the left heart. However, if a substance that provides contrast echoes in the left heart were found, it would promise to contribute greatly to noninvasive diagnosis.

<Problems To Be Solved by the Invention>

Accordingly, the first object of the present invention is to provide a contrast agent for ultrasonic diagnosis which always provides satisfactory contrast echoes.

The second object of the present invention is to provide a contrast agent for ultrasonic diagnosis which is capable of transversing the pulmonary capillaries and providing contrast echoes in the left heart.

The third object of the present invention is to image the coronary arteries in order to diagnose sites of myocardial ischemia by aortic injection of the agent. The invention would therefore provide a contrast agent for ultrasonic diagnosis which can be used as a myocardial contrast echo agent.

<Means of Solving the Problems>

In order to achieve these objectives, the present invention is characterized by the fact that it is an emulsion composed primarily of perfluorocarbon having an emulsion particle size ranging from 1 to 10 μm.

The perfluorocarbons to be used in the present invention are not particularly restricted; any known perfluorocarbons may be used. However, perfluorocarbons having 9-11 carbon atoms are preferred because those with 8 or less readily injure the lungs, and those with 12 or more have a considerable residence time in endothelial cells of the viscera. Preferred are perfluorodecalin, perfluorotripropylamine, perfluoro-4-methylquinolizidine, perfluoro-N-methyldecahydroquinoline, perfluoro-N-methyldecahydroisoquinoline, and perfluoro-N-cyclohexylpyrrolidine. Such perfluorocarbons may be used singly or in combinations of 2 or more, including isomers.

There are no restrictions on the principal emulsifier to be used in the present invention, provided that it is a conventional one. Preferred examples include, phospholipids such as egg yoke and soybean phospholipids and nonionic polymeric surfactants (preferred molecular weight 2000-20,000) such as poly(oxyethylene)-poly(oxypropylene) copolymers.

To manufacture the emulsion of the invention, a crude emulsion is prepared by adding the perfluorocarbon to a predetermined amount of salt solution (for example, a well known isotonic salt solution such as lactated Ringer's solution) containing 1-6 w/v% of the principal emulsifier (preferably 2-5 w/v%) to bring the perfluorocarbon content in the principal emulsifier to 25-100 w/v% and then [emulsifying] with a mixer. This crude emulsion is then homogenized using an emulsifier apparatus to achieve a particle size of 1-10 μm, preferably 2-5 μm.

The emulsification is carried out for 1-30 min under conditions of 5-50 kg/cm² of emulsification pressure and ambient temperature of 50-60°C. Additives that may be used include 0.001-0.1% of an emulsion aid such as a fatty acid, fatty acid salt, fatty acid ester, or polyhydric alcohol, 0.002-0.006% of an antioxidant such as vitamin E, and an agent such as sodium chloride, saccharide, or sorbitol to make [the emulsion] isotonic.

An additional step for making the particle size uniform, such as centrifugation, may be performed after the emulsion is produced. After packaging, the final preparation is obtained following heat sterilization.

The contrast agent of the invention obtained in the above-described manner is suitable for use in applications such as ultrasonic imaging of blood flow patterns. It is administered by injection into an artery or vein that is appropriate for imaging sites such as the left ventricle, right ventricle, aorta, or pulmonary artery. It is usually used in amounts of 5-20 mL per injection. It may be injected as a bolus or continuously together with a physiological saline solution, glucose solution, or the like via a catheter with a three-way stopcock or a chronically indwelling needle.

<Working Examples>

Working and experimental examples are used herein below to describe the present invention more concretely, but the present invention is not limited to these examples.

Working Example 1

150 mL of purified water was added to 15 g of purified egg yolk phospholipids, which were suspended using a mixer; 125 g of perfluoro-N-methyldecahydroisoquinoline was then added.

A prepared solution of 60 mg of monosodium phosphate, 280 mg of disodium phosphate, and 21.8 g of sorbitol in 100 mL of purified water was added; a crude emulsion was obtained using a mixer and brought to a volume of 500 mL with purified water. A uniform emulsion was then obtained by emulsifying this crude emulsion at an emulsification pressure of 10 kg/cm² and temperature of 55 ± 5°C for 10 min, using a Manton-Gaulin emulsifier.

This emulsion was packaged in vials, the air was replaced with nitrogen, and the emulsion was sterilized at 121°C for 5 min.

Working Example 2

A uniform emulsion was obtained in the same manner as in Working Example 1, except that 250 g of perfluoro-N-methyldecahydroisoquinoline was added.

Working Example 3

A uniform emulsion was obtained in the same manner as in Working Example 1, except that 500 g of perfluoro-N-methyldecahydroisoquinoline was added.

Working Example 4

A uniform emulsion was obtained in the same manner as in Working Example 1, except that the emulsification time was 3 min.

Experimental Example

Catheters were inserted in adult dogs to various injection sites via the carotid vein and carotid artery. 5 mL of a contrast medium was injected as a bolus via a catheter, and the imaging effect in echocardiography of the left heart was studied.

The results are shown in Table 1. No fluctuations in heart rate, blood pressure, or electrocardiogram were observed when the contrast agents were injected as a bolus in this experiment, demonstrating that the safety of the agent is sufficiently high in dogs. Echo contrast agents containing air bubbles have been plagued with safety problems in clinical use; furthermore, the administration of hypertonic or highly viscous solutions affects the heart. However, the contrast provided by [the agent of] the invention is extremely useful for ultrasonic imaging because the agent is isotonic and has a viscosity approximating that of blood.

Table 1

Contrast Agent			Imaging Effect in Left Ventricle			
	PFC Concentration*1	Particle Size	Left Ventricle Injection Site	Pulmonary Artery Injection Site	Right Ventricle Injection Site	
Working Example 1	25%	2–3 μm	++	+	+	±
Working Example 2	50%	3–5μ	+++	+	+	±
Working Example 3	100%	3–5μ	+++	+	+	±
Physiological saline solution	-	-	-	-	-	-
Air bubbles/ Urografin	-	-	+++	-	-	±
PFC emulsion	25	0.1–0.2 μm	+	±	±	±

*1 PFC = Perfluorocarbon

<Effect of the Invention>

As described herein above, the contrast agent for ultrasonic imaging of the invention provides useful effects such as:

(1) Always providing satisfactory contrast echoes;

(2) Providing contrast echoes in the left heart due to its ability to transverse the pulmonary capillaries.

(3) The capability of imaging the coronary arteries, making it possible to search for sites of myocardial ischemia.

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Fluorocarbon emulsions as contrast agents in ultrasonic diagnosis
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